



Armed Forces College of Medicine AFCM



Lipoproteins Metabolism-2

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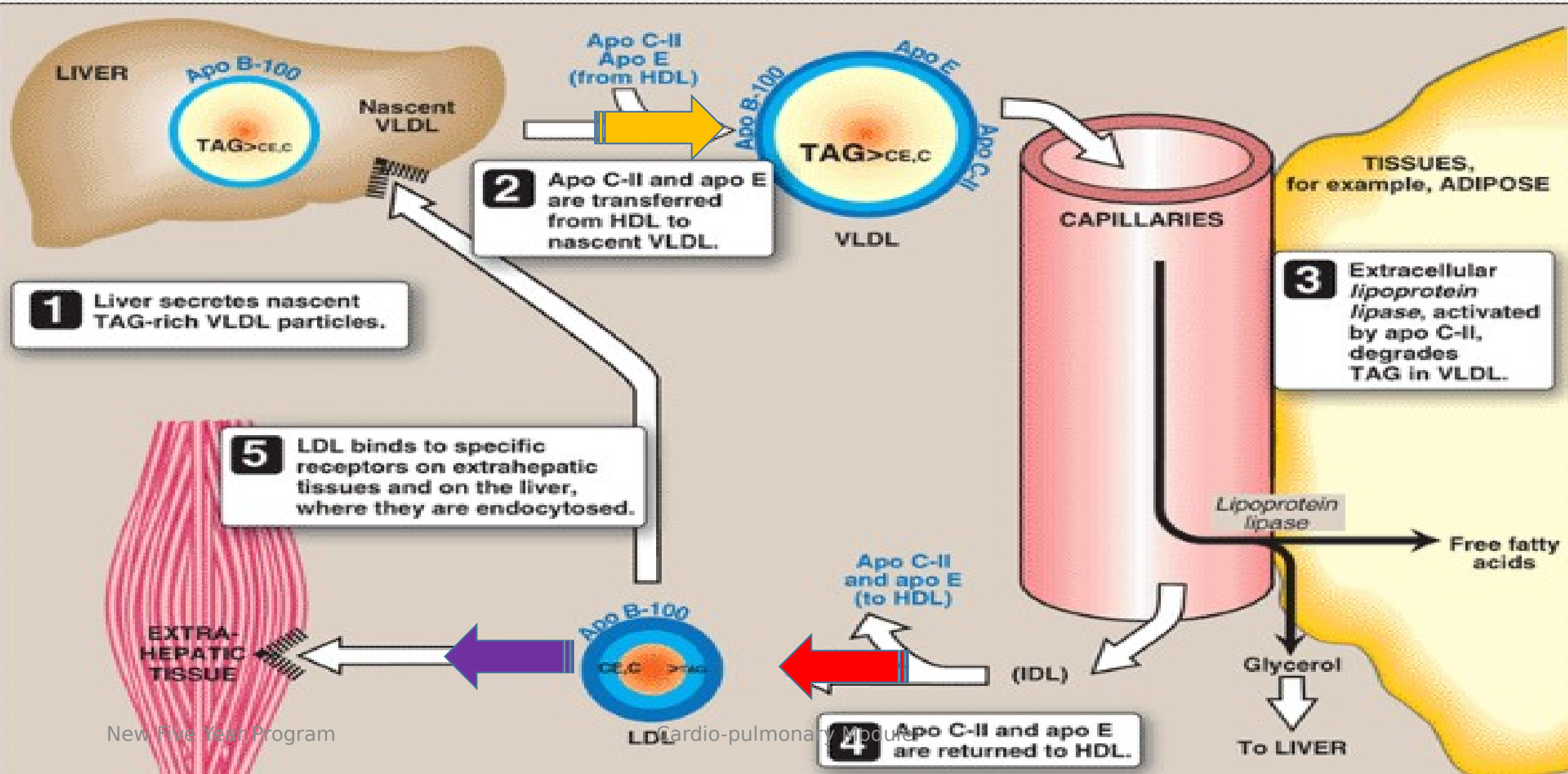
INTENDED LEARNING OBJECTIVES (ILO)



By the end of this lecture the student will be able to:

1. Analyse endogenous TAG transport through VLDL metabolism.
2. Recognize the consequence of imbalance in cholesterol transport and reverse transport
3. Compare between the composition of LDL and HDL
4. Discuss the functions and metabolism of LDL and HDL particles
5. Describe the normal receptor-mediated endocytosis of

Metabolism of VLDL



New Five Year Program

Cardio-pulmonary Module

Very Low Density Lipoproteins (VLDL)



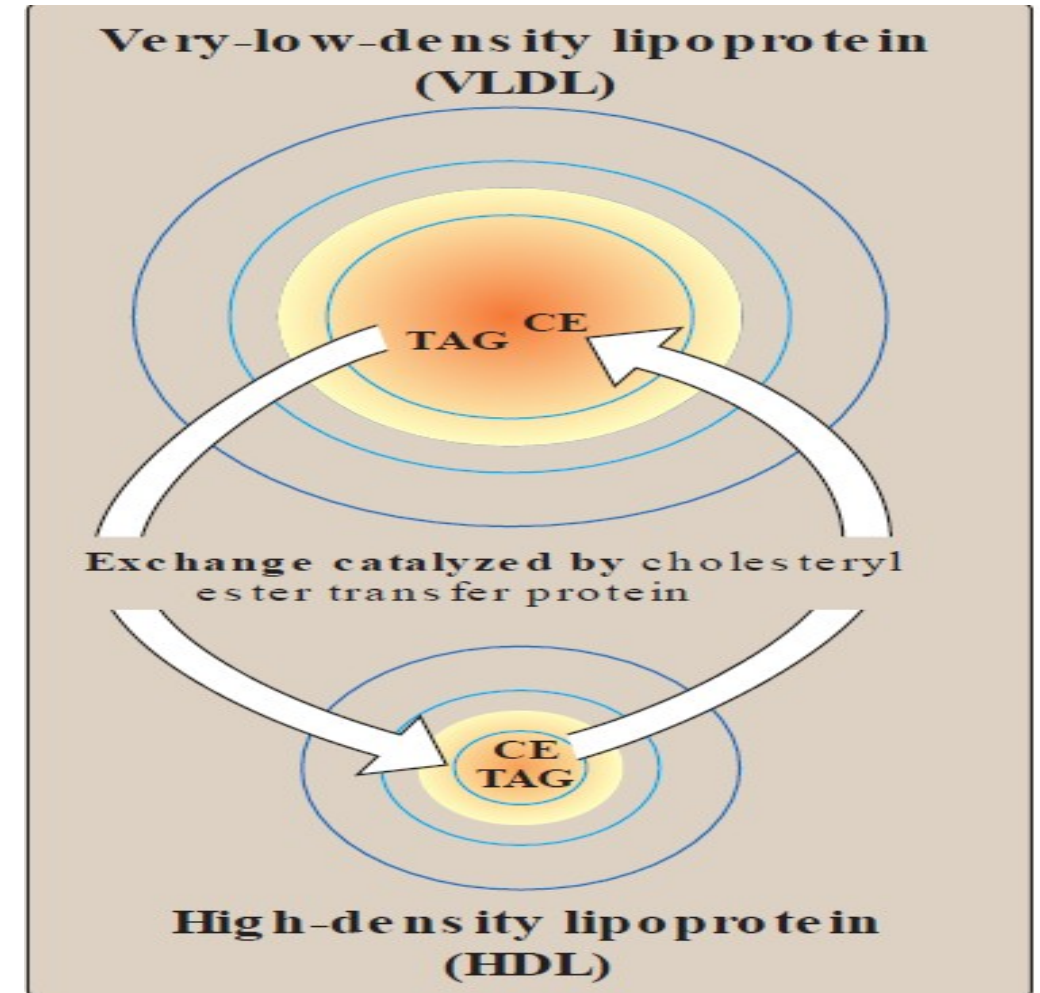
- They are assembled and secreted by the liver into the blood.
- They carry **TAG of hepatic origin** to peripheral tissues.
- **Nascent VLDL**: contains **Apo B-100** (100% of the protein coded by Apo B gene).
- **Mature VLDL**: contain Apo B-100 plus
Apo C-II and Apo E (from HDL)
- **ApoC-II** activates **lipoprotein lipase** that degrades TAG into glycerol and fatty acids. As TAG is degraded, VLDL becomes **smaller in size and more dense.**

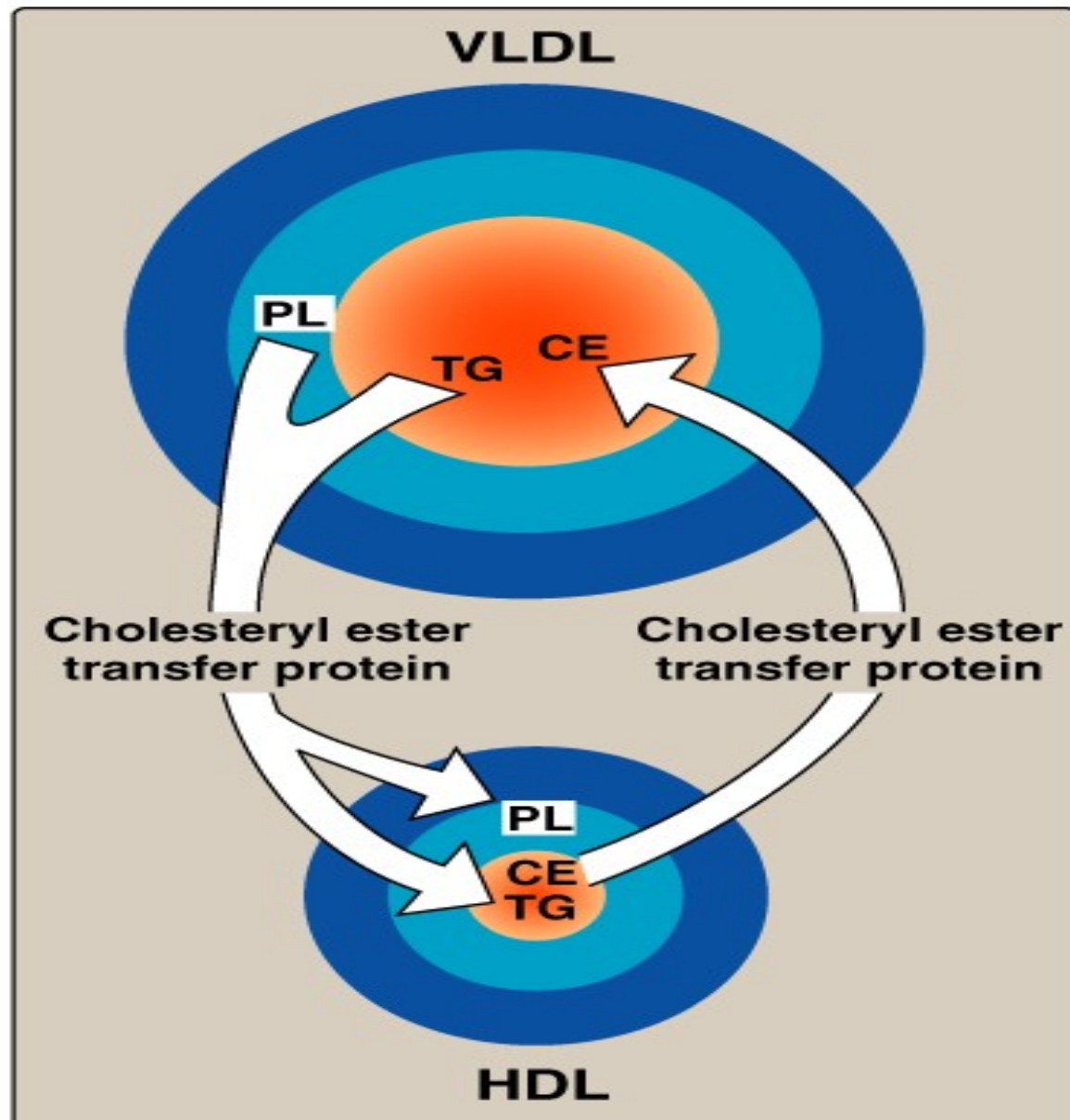
Modification of circulating VLDL



- Apo CII and Apo E return back to HDL
- Transfer of TAG from VLDL to HDL in exchange with Cholesterol Esters (CE) by **cholesterol ester transfer protein**
- VLDL IDL

LDL



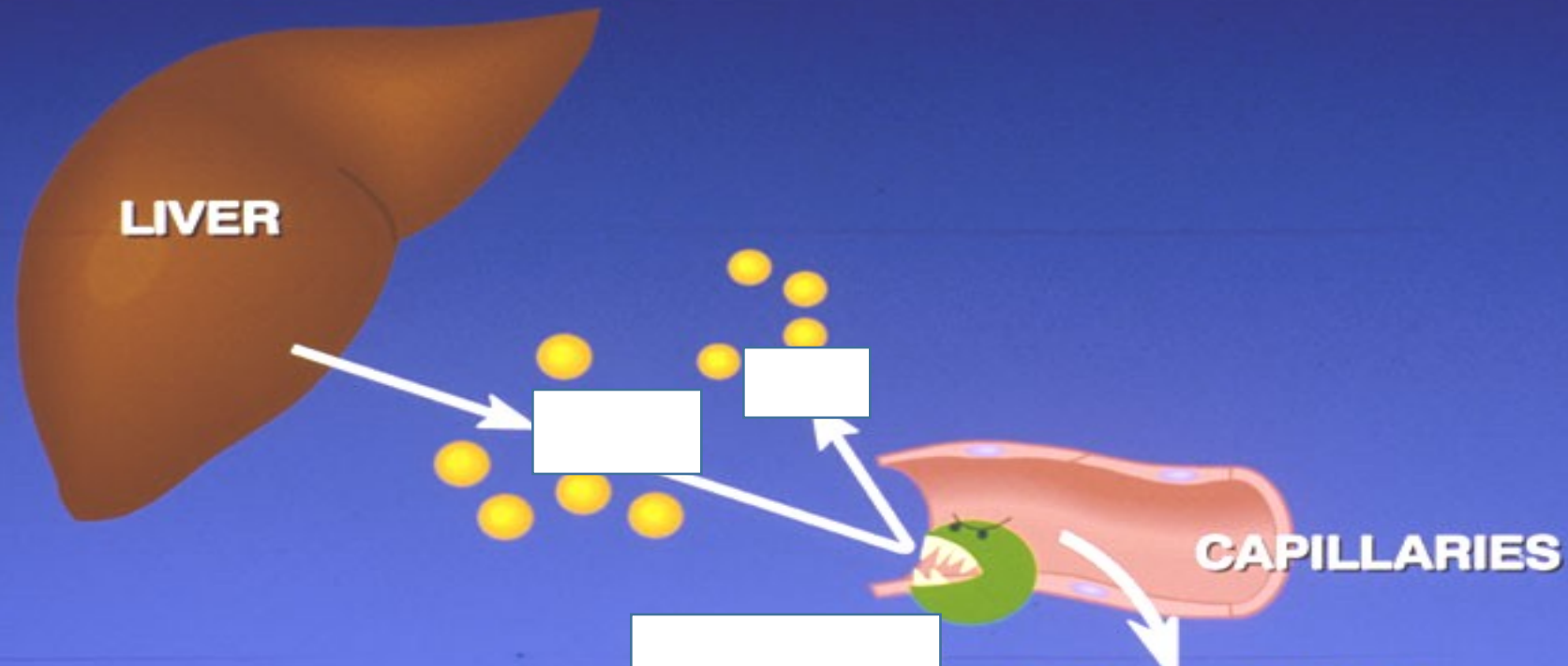


Lipid-Transfer Protein

Lecture Quiz



LIPOPROTEIN PATHWAYS Endogenous (VLDL-IDL)





Metabolism of LDL

Bad lipoprotein



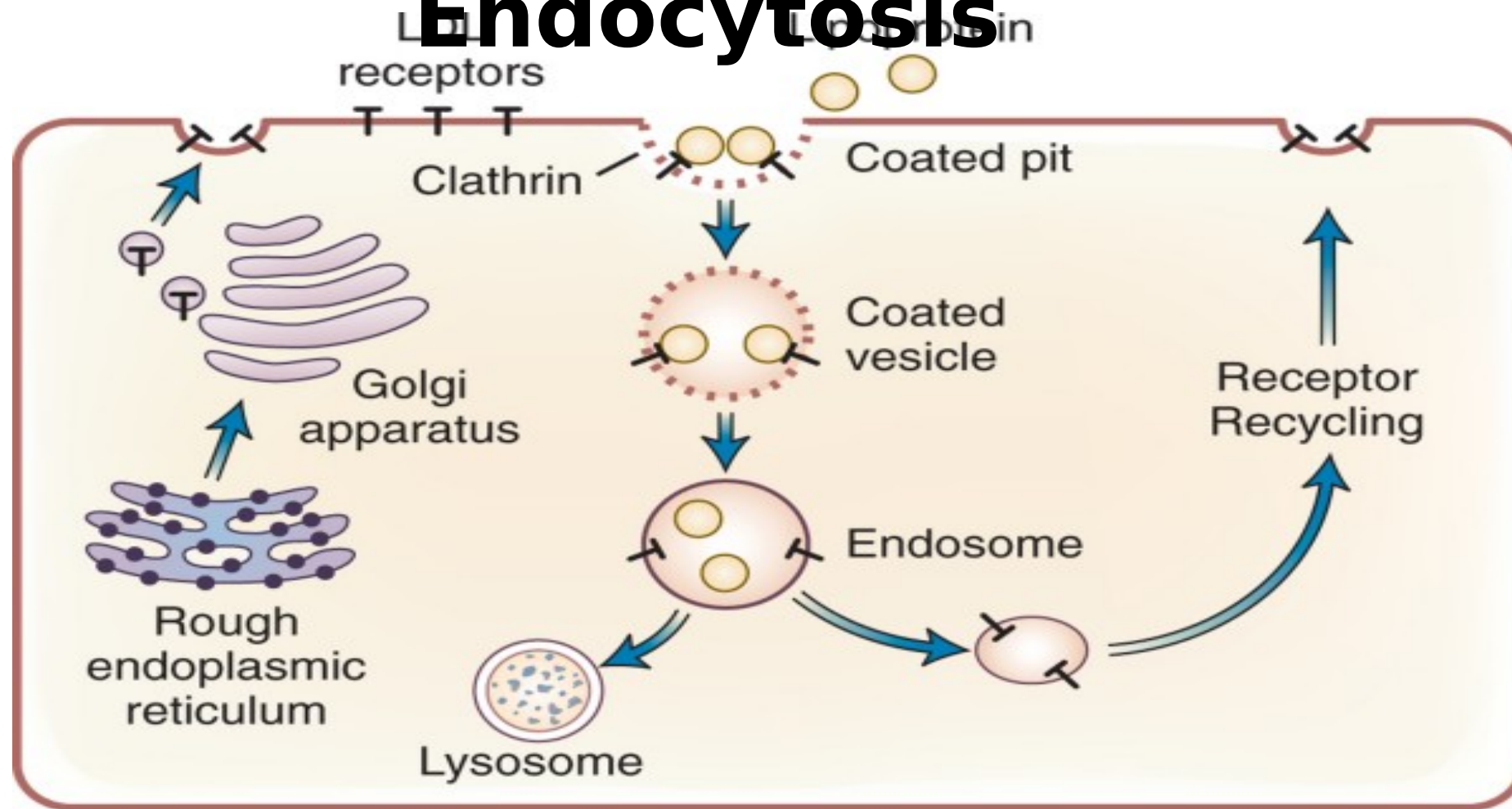
Uptake of LDL



Receptor-Mediated Endocytosis

Macrophage Scavenger Receptors

Receptor-Mediated Endocytosis



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Receptor-Mediated Endocytosis



- ❑ LDL particles contain **less TAG** and **more cholesterol ester** than their VLDL precursors.
- ❑ They provide cholesterol to the tissues by binding to cell membrane **LDL receptors** (in both liver and tissues (that recognize Apo B -100) by **receptor mediated endocytosis**. (which is highly specific and regulated).
- ❑ Another method of uptake of chemically modified

Receptor-Mediated Endocytosis



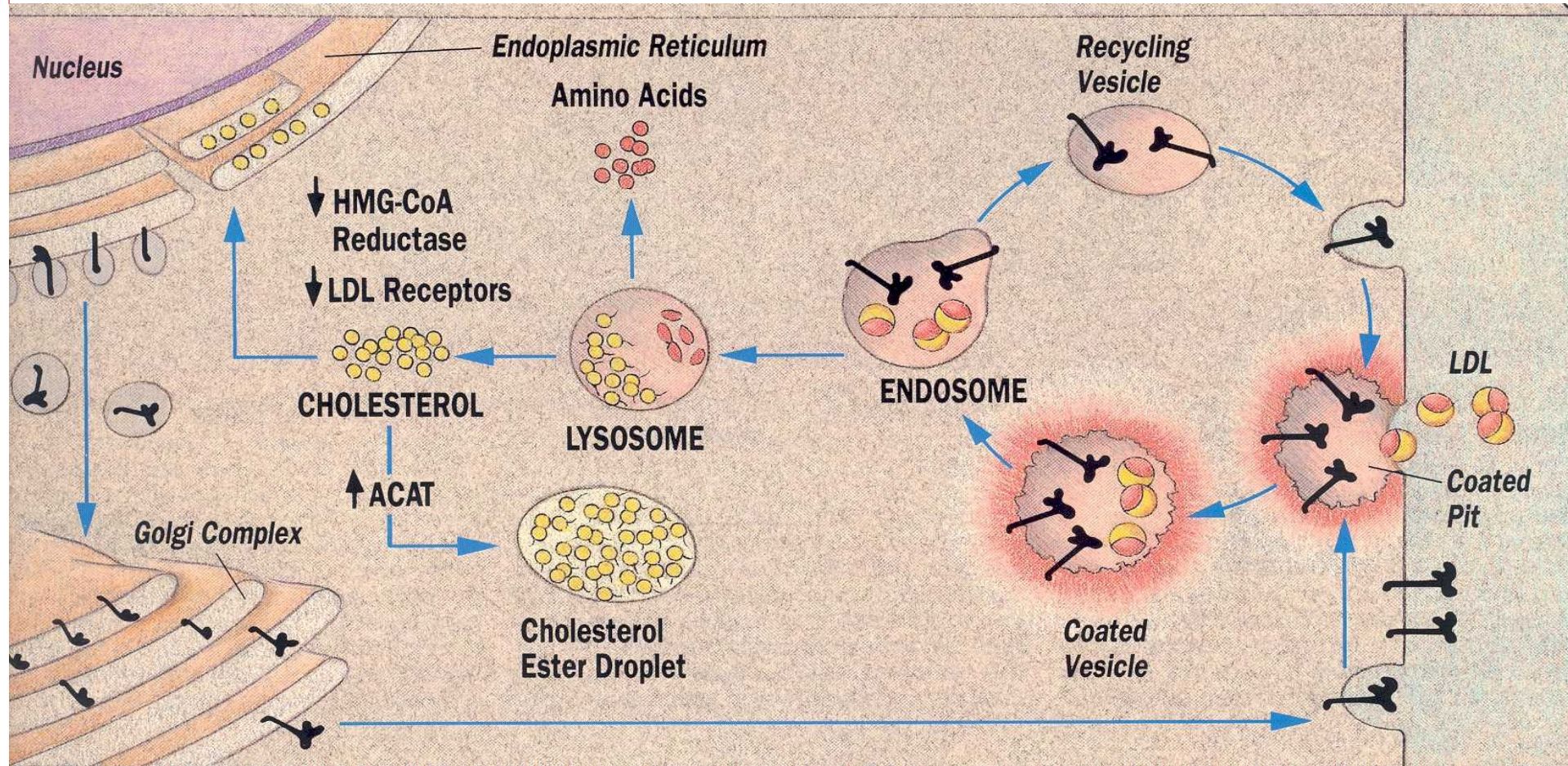
- ❑ **LDL receptors** are -ve charged glycoproteins that are clustered in pits on cell membrane coated with the protein **clathrin** that stabilizes the shape of the pit.
- ❑ LDL-receptor complex is **endocytosed** inside the cells.
- ❑ The vesicle containing LDL rapidly loses its

Receptor-Mediated Endocytosis



- ❑ LDL receptors are **recycled** to cell membrane, whereas LDL in the vesicle are transferred to lysosomes where they are degraded by lysosomal enzymes releasing: **Free Cholesterol, Fatty Acids, Amino acids**. All are utilized by the cell.
- ❑ Excess cholesterol **inhibits synthesis of new LDL** receptors protein thus limiting further

Effects of Endocytosed Cholesterol on Intracellular Homeostasis



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Decrease in cellular uptake of cholesterol



Decrease intracellular levels of cholesterol



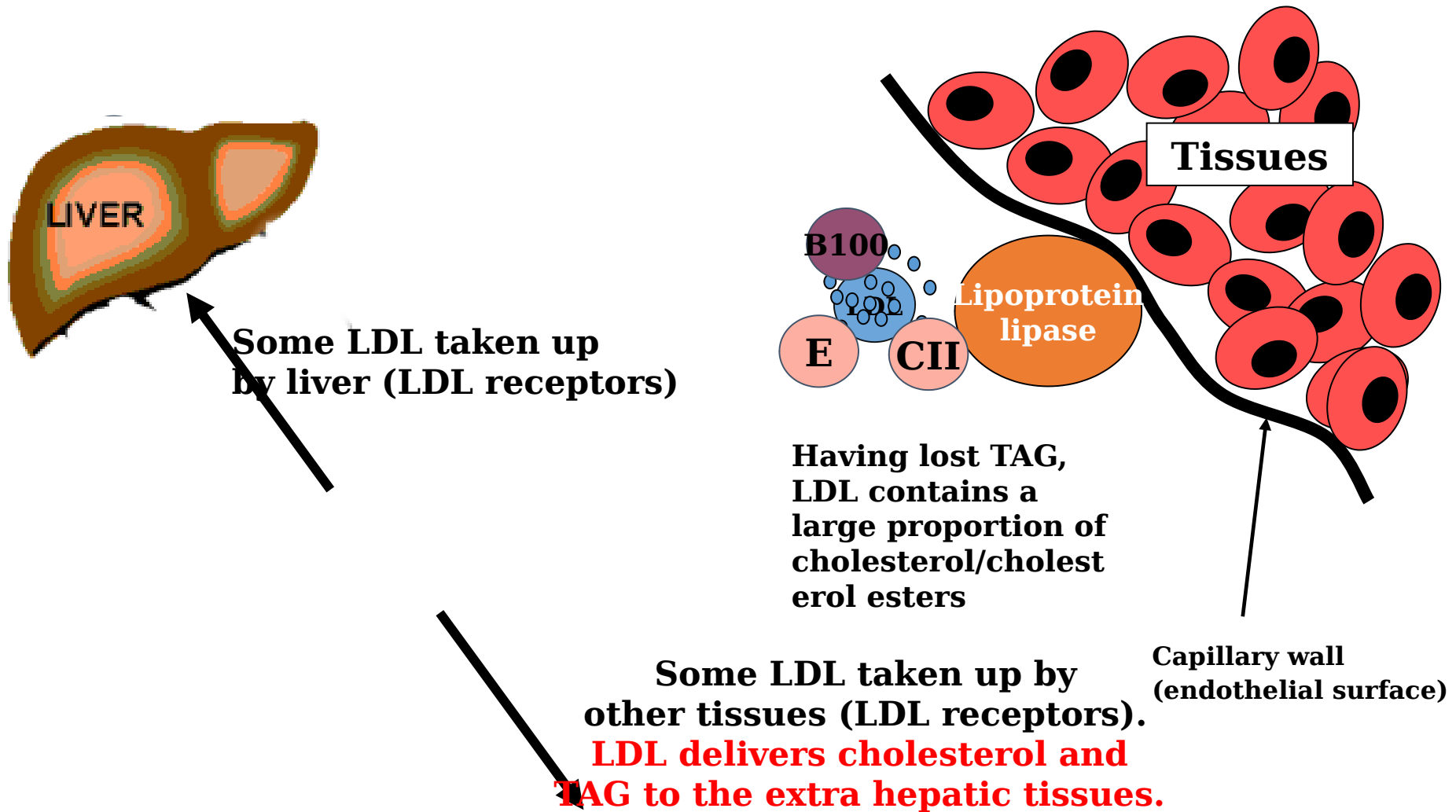
**No feedback inhibition exerted on HMG-CoA
Continuous intracellular synthesis of cholesterol**



More increase in extra cellular Cholesterol

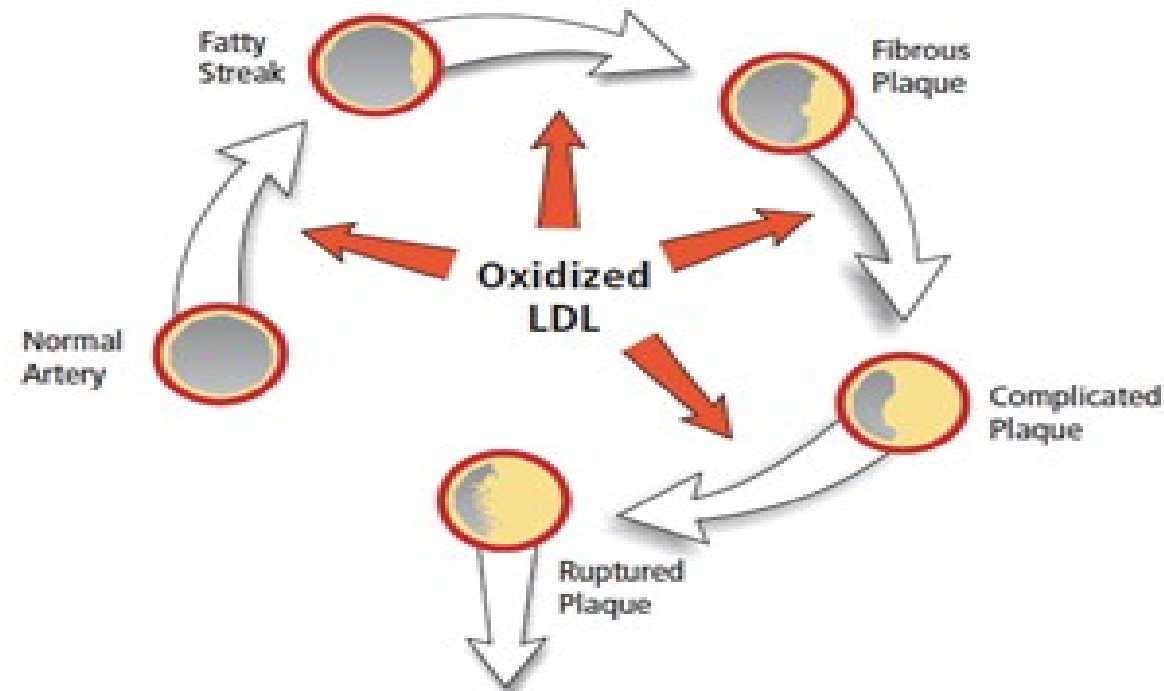


This animation shows how VLDL are metabolised once they enter the circulation from the liver





Oxidized LDL



Atherosclerosis
Ischemic heart
disease

Macrophage Scavenger Receptors



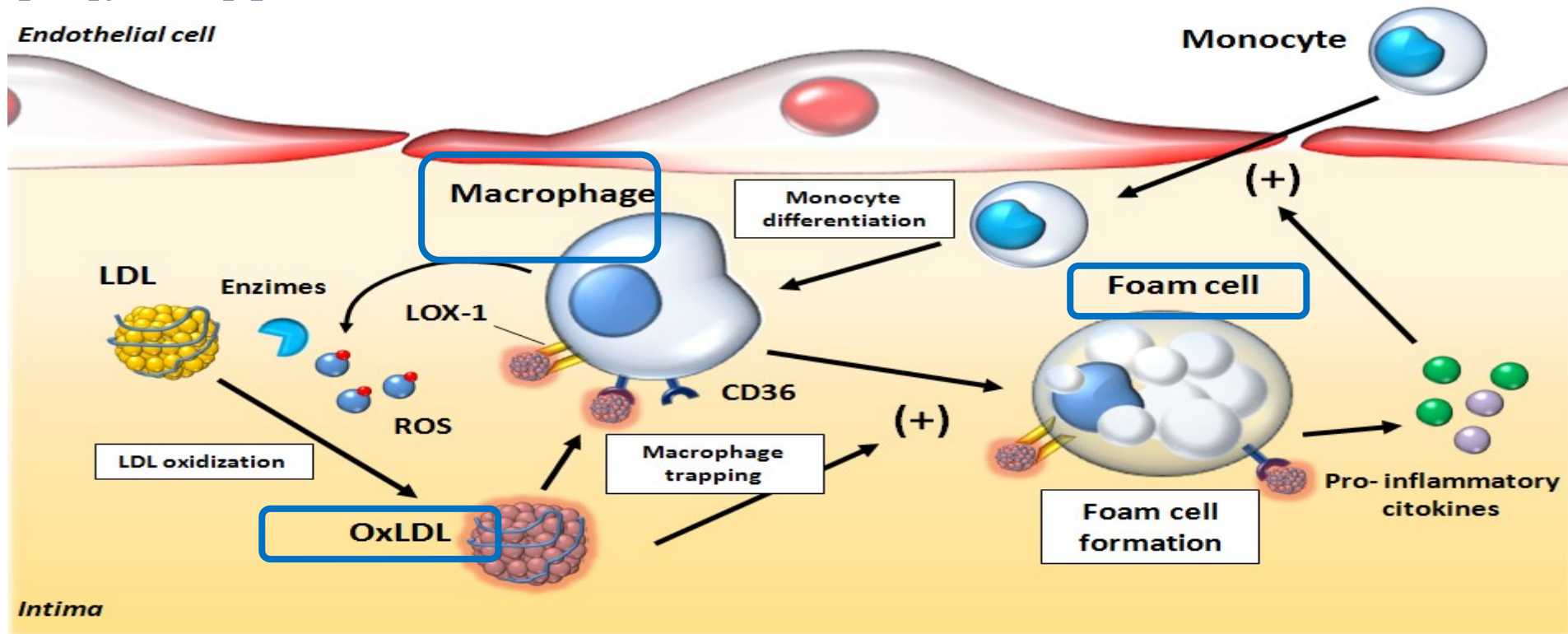
Oxidation of LDL (ox LDL)

- ❑ LDL can be oxidatively damaged: **PUFA's** are oxidized and trigger **oxidation of apoB₁₀₀** protein --> ox LDL.
- ❑ Ox LDL is engulfed by **scavenger receptors** of macrophages in sub-endothelial space which are **not down regulated** in response to increased intracellular cholesterol.
- ❑ **CE accumulate** in these cells and cause their transformation into **foam cells**.

Macrophage Scavenger



layer and lead to the formation of **atherosclerotic plaque**. This leads to narrowing of blood vessels and predispose to **thrombosis** with further ischemia and



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Metabolism of HDL

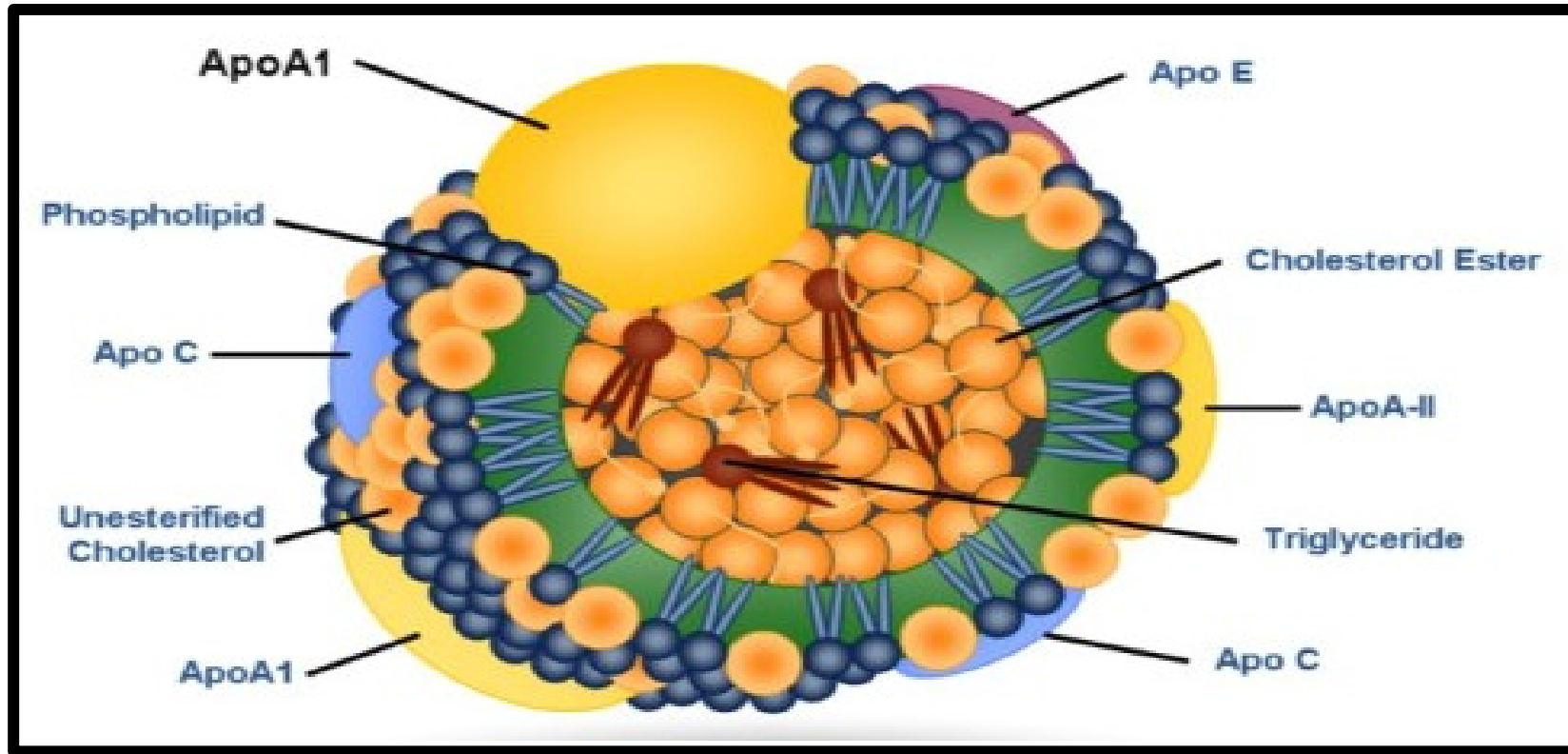
Good lipoprotein



HDL Metabolism



- ❑ HDL is the main transport of cholesterol from peripheral tissues to the liver
(reverse cholesterol transport)
to be excreted through bile.
- ❑ The concentration of HDL in serum is **inversely** related to incidence of **myocardial infarction**.



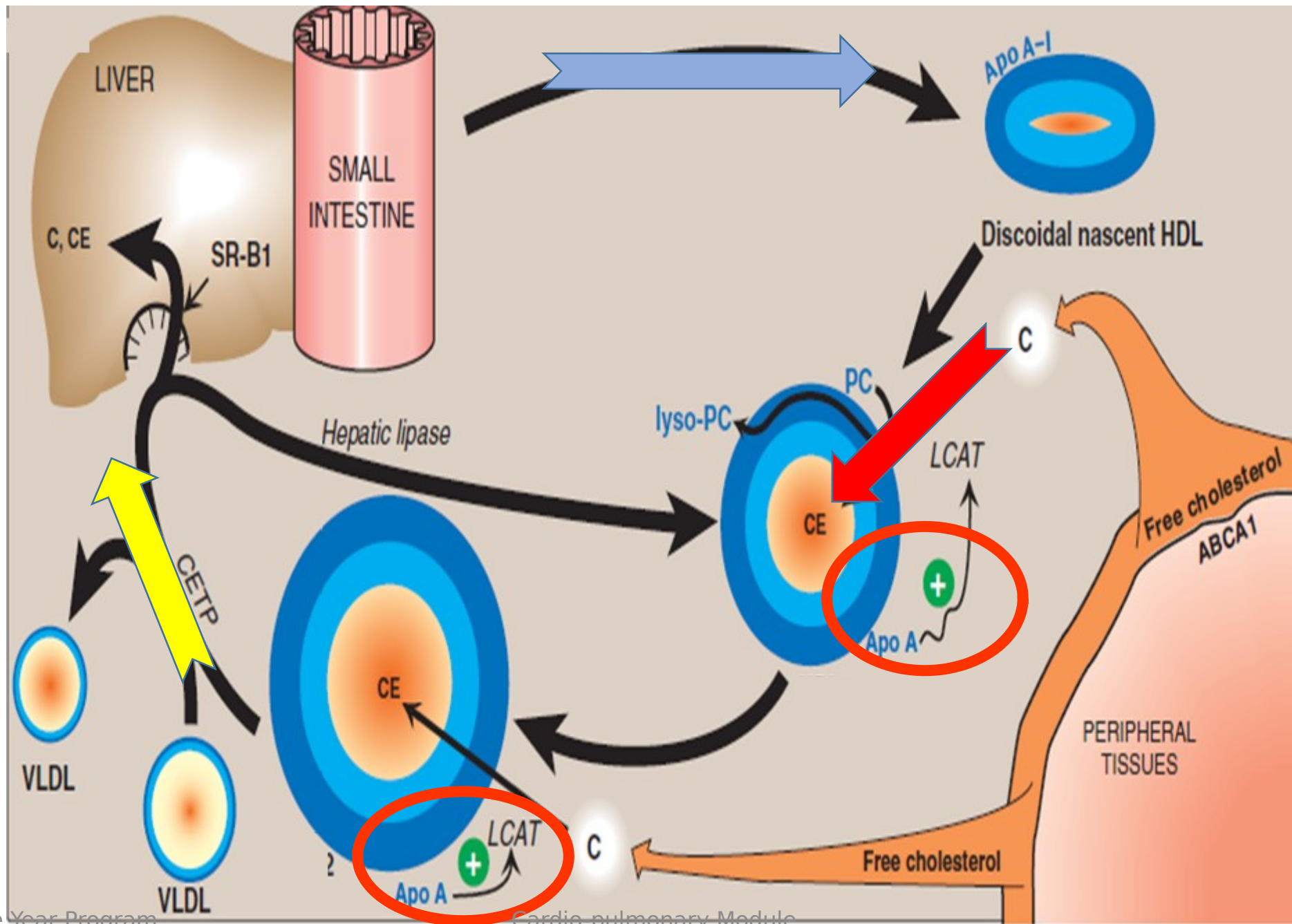
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❑ **Nascent HDL** are disc-shaped particles containing PL mainly phosphatidyl choline and apoproteins **A-1**, **C-II** and **E**.

Apo -1 constitutes about **70%** of apoproteins in HDL.

❑ They are made by liver and intestine and secreted in blood.





❑ They are rapidly converted to **spherical particles** as they accept cholesterol from membranes of tissue cells.

❑ When Cholesterol is taken up by HDL, it is immediately esterified by the plasma enzyme **LCAT** (Lecithin : Cholesterol Acyl Transferase).



❑ **LCAT** is synthesized by liver and binds to nascent HDL.



❑ LCAT transfers **FA from lecithin** to cholesterol producing **hydrophobic cholesterol ester** which is sequestered in the core of HDL .

❑ Lecithin is converted to lysolecithin that bound to serum Albumin

❑ By time, HDL increases in size by accumulating cholesterol esters inside its core.

❑ Finally HDL is up taken **by the liver cells** by a cell-surface receptor protein called **scavenger receptor**

The major functions of HDL are:



- 1. Reservoir for apolipoproteins:**(apo C-II and apo E).
- 2. Uptake of unesterified cholesterol:** Nascent HDLs are discoid containing PL and apo A, C, E. As they accumulate cholesterol, they acquire a spherical shape
- 3. Esterification of cholesterol:** The enzyme LCAT esterifies cholesterol once it is taken up by HDL. The enzyme is synthesized by the liver and activated by apo A-I.
- 4. Reverse cholesterol transport This process involves:**
 - a. efflux of cholesterol from peripheral cells to HDL
 - b. Esterification of cholesterol by LCAT
 - c. Binding of CE-rich HDL (HDL2) to liver (bile) and steroidogenic cells (Steroid H)
 - d. Selective transfer of CE to these cells and release of CE-depleted HDL (HDL3)

ATP-binding cassette (ABC) proteins

- ABC are transport proteins using **energy** (ATP hydrolysis) to transport materials in and out of cells and across intracellular compartments.
- The efflux of cholesterol from peripheral cells is partly mediated by ABCA1
- Tangier disease (very rare)

Deficiency of ABCA1

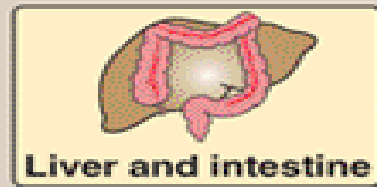
No HDL (due to degradation of lipid-poor apo A-1)



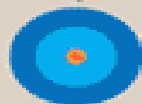
There are many types of apolipoproteins

Apoprotein	Lipoproteins	Function(s)
Apo B-100	VLDL, IDL, LDL	1) Secretion of VLDL from liver 2) Structural protein of VLDL, IDL, and HDL 3) Ligand for LDL receptor (LDLR)
Apo B-48	Chylomicrons, remnants	Secretion of chylomicrons from intestine
Apo E	Chylomicrons, VLDL, IDL, HDL	Ligand for binding of IDL & remnants to LDLR
Apo A-I	HDL, chylomicrons	1) Major structural protein of HDL 2) Activator of LCAT
Apo A-II	HDL, chylomicrons	Unknown
Apo C-I	Chylomicrons, VLDL, IDL, HDL	Activation of LCAT
Apo C-II	Chylomicrons, VLDL, IDL, HDL	Activator of LPL
Apo C-III	Chylomicrons, VLDL, IDL, HDL	Inhibitor of LPL activity

Lipoproteins



generate



HDL

composed of

Lowest TAG
High cholesterol

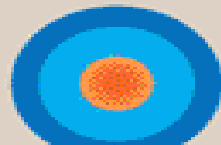
functions to

Deliver cholesterol
to the liver for
elimination



VLDL

generates



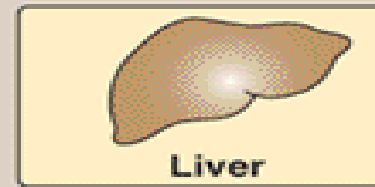
LDL

composed of

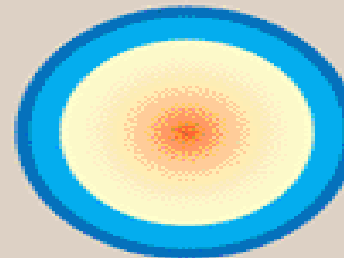
Low TAG
Highest Cholesterol

functions to

Deliver cholesterol
to the peripheral
tissues and to liver



generates



VLDL

composed of

High TAG
Low cholesterol

functions to

Deliver de novo
TAG to peripheral
tissues



generates

Chylomicrons

composed of

Highest TAG
Lowest cholesterol

functions to

Deliver dietary
TAG to peripheral
tissues



Low density lipoprotein (LDL) is concerning to transport mainly:

- a. Exogenous TG
- b. Endogenous TG
- c. Free fatty acids
- d. Cholesterol from liver to other tissues.
- e. Cholesterol from peripheral tissues to liver

Take home message

- Nascent VLDL are produced in the liver, they contain apo B-100, and carries endogenous (hepatic) TAG to the peripheral tissues.
- Mature VLDL contains also apo C-II and apo E from HDL. Lipoprotein lipase degrades TAG within the chylomicrons and the VLDL.
- VLDL receives cholesteryl esters from HDL by cholesteryl ester transfer protein. VLDL is converted to IDL, then to LDL.

Take home message

- Plasma LDL is the bad cholesterol carrier, while the HDL is the good cholesterol carrier.
- LDL and HDL differ in their metabolism, structure, and function.
- The pathogenesis of atherosclerosis includes the uptake of oxLDL by macrophage through scavenger receptor class A (SR-A) forming foam cells and eventually atheromatous plaque.
- HDL particles are assembled in liver and intestine and secreted as nascent disc-shaped HDL particles. Mature HDL (HDL2) contains cholesteryl ester and is spherical

SUGGESTED TEXTBOOKS



1. Lippincott's illustrated reviews in Biochemistry (6th edition) p.227-237 for cholesterol and steroid metabolism.
2. National Institutes of Health (NIH) Publication No. 01-3305 May 2001 (National Heart, Lung, and Blood Institute) Adult Treatment Panel III (ATP III) guidelines included in the National Cholesterol Education Program (NCEP) report, ATP III Guidelines At-A-Glance Quick Desk Reference.

Thank you

